REMARKS

I. Scope of Claims.

The instant invention presently contains claims 1, 3-6, 19-22, 35 and 37. Previously presented claims 26-34 and 36 have been withdrawn as being directed to non-elected inventions. Additionally, previously presented claims 2, 23-25 have been withdrawn as being directed to non-elected species. Applicants have amended claim 1 to overcome rejections in the instant office action. Applicants have added claims 38-44 to further define and emphasize their invention. These amendments and newly added claims add no new matter and find support in the originally filed specification and claims.

II. Claim Objections.

The Examiner objected to claim 1 because various terms were not spelled out in full. Applicants have amended claim 1 accordingly and ask that this objection be withdrawn.

III. Claims 1, 3-6, 19-22, 35 and 37 rejected under 35 USC 103(a).

The Examiner rejected claims 1, 3-6, 19-22, 35 and 37 under 35 USC 103(a) as being un-patentable over U.S. Patent No. 5,770,222 to Unger et al. (Unger) in view of U.S. Patent No. 7,008,791 to Gregoriadis et al. (Gregoriadis) Applicants respectfully traverse this rejection.

A. Examiner's Rejection: The Examiner's rejection stated that Unger already disclosed a drug delivery system comprising gas-filled liposomes having encapsulated therein a therapeutic drug, wherein at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied. The Examiner further stated that Unger also taught that the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation and the lipid in the gas-filled liposomes may be in the form a single bilayer or a multilamellar bilayer ant that utilized lipids to create liposome microspheres include and not limited to lipids such as DMPC, DPPC, DSPC cholesterol, cholesterol sulfate and cholesterol hemisuccinate and if desired a variety of cationic lipids.

The Examiner acknowledges that Unger does not teach specifically the preparation of a liposome comprising saturated synthetic phosphatidyl cholines selected from the group consisting of DMPC, DPPC and DSPC; cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of DC-Chol, DAC-Chol, DMTAP, DPTAP and DOTAP with a percentage ranging from about 5 to 20 mole-% and one or more selected from the group consisting of protein and peptide active substances.

The Examiner believes that the deficiencies in Unger, acknowledged above, in arriving at Applicants' claimed invention are cured by Gregoriadis. The Examiner reasons that Gregoriadis already disclosed at least a liposome preparation comprising at least a cationic compound such as DOTP or DC-Chol, at least one zwitterionic phospholipids such as DPPC and DSPC and cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components. The Examiner further stated that Gregoriadis further taught that the product liposomes may be multilamellar or unilamellar vesicles.

B. Applicants' Claimed Invention: Applicants' claimed invention, as described in amended claim 1 from which all rejected claims depend, require a depot system having "saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC), cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of 3-β-[N-(N',,N'-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 3-β-[N-(N,,N'-dimethylaminoethane)carbamoyl]cholesterol (DAC-Chol), N-[1-(2,3-dimyristoyloxy)propyl]-N, N, N-trimethylammonium salt (DMTAP), N-[1-(2,3-dipalmitoyloxy)propyl]-N, N, N-trimethylammonium salt (DPTAP) and N-[1-(2,3-dioleoyloxy)propyl]-N, N, N-trimethylammonium salt DOTAP with a percentage ranging from 5 to 20 mole-% in the liposomal membrane, and one or more selected active substances from the group consisting of protein and peptide active substances."

C. Teachings of Cited References: Unger is a disclosure having gas-filled liposome compositions and drugs encapsulated therein. Unger teaches that ultrasonic energy interacts with a gas within a gas-filled microspheres resulting in a burst of the microspheres and allowing a therapeutic agent to be released. In the examples contained within Unger liposomes from DPPC or DPPC/DOTMA or PEG-DPPE or eggPC/DOTMA or DPPC/sodium lauryl sulphate or DSPC

were used. Unlike the instant claimed invention, the disclosed specific liposome compositions of Unger do not comprise cholesterol and the presence of cationic lipids is not mandatory. Furthermore Unger teaches the materials that may be utilize in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.

Gregoriadis discloses oral vaccines comprising a nucleic acid coding for an antigen against which vaccination is desired. Gregoriadis found that liposomal compositions as oral vaccines preferably comprising at least one zwitterionic phospholipid and at least one cationic compound. In a preferred aspect of the invention the zwitterionic phospholipid is a mixture of DSPC and DOPE, a saturated phosphatidylcholine and an unsaturated phosphatidylethanolamine (col. 3, line 15-18). Gregoriadis also mentioned that other components may be included in the liposome forming component, such as cholesterol in amounts up to 50 % by weight. However, Gregoriadis teaches that the liposome forming components are preferably free of cholesterol (see col.4, line 18-19 or Example 2 (col. 8, line 67 – col. 9, line 1-3). Accordingly, the liposomal compositions of Gregoriadis are free of cholesterol.

D. Deficiencies of References: Unger gives a generic disclosure of gas-filled liposome compositions and drugs encapsulated therein. The disclosed specific liposome compositions of Unger do not comprise cholesterol and the presence of cationic lipids is not mandatory. The object of the present invention is to provide stable liposomal depot formulations for protein and peptides that achieve long-term release of an active substance and have good tolerability in an organism. The instant claimed invention comprises saturated phospholipids, such as DSPC, DPPC or DMPC and cholesterol or derivatives and cationic lipids such as DC-Chol, DAC-Chol, DMTAP, DPTAP and/or DOTAP, which are useful as depot systems for the sustained release of active agents. Unlike the disclosure of Unger, the presence of cationic lipid is mandatory, as cationic liposomes undergo aggregation with serum components or interstitial fluid components so that the depot (the liposomes) remain at the site of entry, thus preventing migration of the liposomes, e.g. into the lymph.

Furthermore, the composition of the instant claimed invention is stabilized, even in the aggregated state, by using saturated backbone lipids and cholesterol or derivatives. Hence, a burst release of the depot system can be avoided and a sustained release of the therapeutics over

extended periods of time becomes possible, by using saturated backbone lipids and cholesterol or derivatives.

Unlike the instant claimed invention, the liposomes of Gregoriadis are selected to be stable in the GI tract and to efficiently transfect cells. Gregorriadis actually teaches away from the instant claimed invention, as the compositions of Gregoriadis are preferably free of cholesterol as disclosed in the specification and the examples.

The combined teachings of Unger and Gregoriadis contain no motivation to be utilizing saturated phospholipids, such as DSPC, DPPC or DMPC and cholesterol or derivatives and cationic lipids such as DC-Chol, DAC-Chol, DMTAP, DPTAP and/or DOTAP, as Applicants have disclosed and claimed.

Since the composition within Applicant's disclosed and claimed invention is not found or suggested anywhere within the art, it appears that in creating his obviousness rejection that the Examiner gleaned knowledge form the Applicants' disclosure contrary to the holding of *In re McLaughlin*. Applicants respectfully request that the rejected claims be reconsidered in light of well-established legal principles, which provide,

> "*That one skilled in the art is not synonymous with obviousness.... That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the reference to make the claimed invention" Ex parte Levengood, 28 USPQ 2d 1300 (Bd. Pat. App. & Inter. 1993).*

The particular combination of teachings that the Examiner suggests, in hindsight with the benefit of Applicants' disclosure, in an attempt to arrive at the Applicants' claimed invention, is neither taught nor suggested by either cited reference either alone or in combination. Unger or Gregoriadis do not disclose or suggest Applicants' disclosed and claimed composition of a depot system having "saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC), cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of 3-β-[N-(N',,N'-dimethylaminoethane)carbamoyl]cholesterol (DC-Chol), 3-β-[N-(N,,N'-dimethylaminoethane)carbamoyl]cholesterol (DAC-Chol), N-[1-(2,3-dimyristoyloxy)propyl]-N,

N, N-trimethylammonium salt (DMTAP), N-[1-(2,3-dipalmitoyloxy)propyl]-N, N, N-trimethylammonium salt (DPTAP) and N-[1-(2,3-dioleoyloxy)propyl]-N, N, N-trimethylammonium salt DOTAP with a percentage ranging from 5 to 20 mole-% in the liposomal membrane, and one or more selected active substances from the group consisting of protein and peptide active substances…," as Applicants have disclosed and claimed in amended claim 1 from which all rejected claims depend.

Furthermore, neither Unger nor Gregoriadis provide "sufficient impetus" to support their combination that the Examiner makes to effect the obviousness rejection. In fact Gregoriadis actually teaches away their combination to arrive at a composition having cholesterol as Applicants have disclosed and claimed. Importantly, this combination does not arrive at Applicants' claimed invention. Applicants' claimed invention is patentably distinct from that of Unger, as Examiner has acknowledged, alone or in combination with Gregoridaris as neither, alone or in combination, suggest a composition having a "saturated synthetic phosphatidyl choline… and cationic lipids, cholesterol and/or derivatives…" as Applicants have disclosed and claimed in amended claim 1, from which all rejected claims depend. Applicants respectfully requests that this rejection be withdrawn.

CONCLUSION

For at least the reasons set forth above, reconsideration and allowance of this application are believed to be in order, and such action is hereby solicited. If any points remain an issue which the Examiner feels may be best resolved through a telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below. The Examiner is invited and encouraged to telephone the undersigned with any concerns in furtherance of the prosecution of the present application.

Please charge any deficiency as well as any other fee(s) which may become due at any time during the pendency of this application, or credit any overpayment of such fee(s) to Deposit Account No. 50-2896.

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Respectfully submitted,

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